REMARKS/ARGUMENTS

At the time of the instant Office Action, claims 1, 3, 5-14, 16, 17 and 32 were pending in the application. Claims 5, 7, 13 and 32 have been cancelled. Claims 1, 3, 5-12, 14, 16, 17 stand rejected. Applicant respectfully traverses the rejections and offers the following amendments and arguments in response.

Claim amendments

Claim 1 is amended to introduce the term topical into the preamble. Support for this can be found at least in [0008], [0029] and [0040]. The term base has been substituted for the term "buffer" in order to more clearly define the role of the amine. Trometamol has been removed from the group of organic amines.

Claim 6 has been amended to remove trometamol from the claim and to remove the term "about" from the ranges for the amines.

Claims 8, 12, 16 and 17 have been amended to remove the term "about" from the claims.

Claim 10 has been amended to remove the phrase "at least one of" for grammatical correction.

No new matter is presented in making these amendments.

Claim rejections – 35 USC § 112

Claim 32 is rejected under 35 USC 112, second paragraph, and in response, Applicant has now cancelled.

Claim rejections – 35 USC § 103

Examiner argues that " ... *Said diclofenac is taught as being present in an amount of 0.1 to 0.2 % (see entire document, for instance claim 1, also note percentages in table 1 of instant specification). Said tromethamine is exemplified as being present in an amount of approximately a third of that of the diclofenac (see for entire document, for instance page 2, lines 13-17, note that the instant claims utilize the term "about" with regard to the amount of tromethamine present. Pinza fails to directly teach that the non-steroidal anti-inflammatory drug is flurbiprofen."*

More to the point, Pinza teaches only "the salt of diclofenac with tromethamine" and no other NSAIDs. Examiner is attempting to extend the "obviousness" of an easy "substitutability" or "substituting equivalent" of a specific NSAID with any other, more specifically, that diclofenac tromethamine salt (Pinza) may be substituted for any other NSAIDs including flurbiprofen.

Examiner goes further with the "substitutability theory" when he reports again that: *"Caldwell teaches an oral composition comprising a non-steroidal antiinflammatory, specifically, diclofenac, flurbiprofen, naproxen, or ketoprofen (see entire document, for instance claims 1 and 3). Caldwell further teaches the use of TRIS (tromethamine) buffer in said composition (see entire document, for instance examples 9 and 10)."*

In Caldwell TRIS (tromethamine) is present with flurbiprofen but Examiner fails to consider that "*The compositions offer the formation of finely dispersed active ingredients upon dispersion in gastric juice*" and that Caldwell teaches that *"(e) a pharmaceutically acceptable quantity of a dispersing agent*" (Claim 1) regardless that: "dispersion" is not a "solution" (invention). Dispersion is intended for the "gastric juice" and not for oromucosal or topical purposes as is the present application. Furthermore, the pH of gastric juice is about 1.2 while the physiological pH of mouth the is between 6.7 and 7.5 making these two very different applications.

Therefore Caldwell fails to teach that the described and claimed composition is a "solution (the word "solution" is absent) and fails to describe any pH range of the dispersion (the word pH referring to the dispersion is also absent). Even the word "water" is absent in the claims of the dispersion. While the instant invention claims a "throat, mouth and/or gum sprayable *topical* pharmaceutical preparation in the form of an aqueous solution, Caldwell does not even mention the words throat, mouth, or gums.

Examiner suggests that Applicant would have been motivated to combine ingredients described at random in prior art (Pinza, Caldwell, Lundberg) and to organize them in a "*third composition for the exact same purpose*". However, Examiner fails to offer any evidence or proof that this "substitutability" has any objective support. By contrast, scientific findings and international publications support the opposite of Examiner's theoretical hypotheses, as Applicant will better illustrate.

As an initial matter, the substitutability of a hydrogen pump inhibitor with a NSAID represents an overextension of the obviousness doctrine. The myriad differences between the indications and the types of chemical structures involved are too numerous to detail, but suffice it to say that one would not be motivated with a reasonable outlook of success to make this substitution. The fact that two molecules have been approved by the FDA for use in humans is not proof of their interchangeability, particularly when they have different (and in the case of NSAIDs, even contra-indications as they have been shown to increase gastric acidity).

"Substitutability of Flurbiprofen with diclofenac (or its salts)

Even one lacking skill in the art recognizes that there are several differences of structure, characteristics and pharmacological properties supporting the "non-substitutability of flurbiprofen with diclofenac and of diclofenac with other NSAID's.

Different Chemical characteristics and pharmaco-toxicological properties (Flurbiprofen versus Diclofenac and its salts)

As an initial matter, NSAIDs are often classified based on their derivative structure, one such classification of NSAIDs is termed "Propionic acid derivatives" (such as flurbiprofen) while another is "acetic acid derivatives," where diclofenac is included. This is a basic chemical difference. This classification has been used to demonstrate differences between the classes of NSAIDs (flurbuprofen on one side and diclofenac on the other) in for example bone mineral density (BMD) amongst NSAID users. (Nonsteroidal anti-inflammatory drugs and bone mineral density in older women: the Rancho Bernardo study, J. Bone Miner. Res. 1998 Dec; 13(12): 1924-31). In this study, there was a significant difference between the two classes emphasizing not only the real differences between the classes but also the *non-substitutibility* of diclofenac for flurbiprofen.

However, sometimes there are substantial differences not only among the different families of NSAIDs, but also with the pharmacol-toxicological properties due to different administration routes, such as in the case of diclofenac sodium topical gel 1% sodium for which there is an FDA-Health and Human Services alert reporting the side effects of diclofenac sodium topical gel 1%. See FDA alert directly at:

http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm193047.htm

No similar safety information (FDA alert) is available for flurbiprofen or for topical flurbiprofen, so that "clinical tolerance" represents another significant difference supporting that flurbiprofen cannot be simply substituted by diclofenac (Pinza) in the presence of the aforesaid alert, even for topical use, particularly when the use of the considered NSAID is intended for oromucosal topical use.

In addition, the different behavior of Cytochome P450 3A Enzymes in Cynomologus Monkeys and Humans (Reference 20) represents a pharmacological effect of flurbiprofen different from diclofenac in the same species and also in very close species (Cynomologus Monkeys and Humans). Those findings evidences that there are sophisticated pharmacological differences among the two NSAIDs so that it would not be reasonable to support any kind of substitutability of flurbiprofen with diclofenac.

In conclusion, there is a lack of evidence that would justify the substitutability of flurbiprofen with diclofenac, while, by contrast, there are several findings supporting the substantial chemical, toxicological and pharmacological differences. This is without stating obvious differences such as distinct solubility profiles, and a lack of predictable solubility profiles at certain critical pH ranges. These very often teach away from expected or predictable results, which therefore are not obvious. Facing such critical distinctions, it appears illogical that flurbiprofen in the presence of meglumine on one side and diclofenac tromethamine on the other side may represent a case where the two composition could show the "*exact same purpose*".

Diclofenac and differences among its salts

Apart from diclofenac sodium (a salt of an inorganic acid) which is the most widely used, there are other organic salts of diclofenac described in the interesting article titled "Preparation and characterization of a range of diclofenac salts" (Reference 22).

In this publication eight (including five novel) different counterions of diclofenac are prepared and studied, and among them there is also diclofenac TRIS (Table I, page 165), the same tromethamine salt described in Pinza. The abstract on the front page firstly indicates that "*Four of bases used to prepare these salts were*

related in the chemical structure, differing only in the number of hydroxy groups". They are listed in the same Table 1 as AMP, AMDP, TRIS (tromethamine) and DNL salts.

Table 3 summarizes Melting point (C°), Solubility (mM), pH and Intrinsic dissolution rate of those different diclofenac salts. Melting points and Intrinsic dissolution rate are surprisingly very variable (significantly different from expected), but the most surprising difference is the solubility of diclofenac salts, where (see Abstract in the front page) "*The aqueous solubilities of the salts studied ranged from 3.95 mM (tris(hydroxymethyl)aminimethane salt) to 446 mM (deanol salt), corresponding to a 113-fold difference is solubility.*" In fact, diclofenac DNL is 113-fold more soluble than diclofenac TRIS (tromethamine) described in Pinza. It would be obvious that Pinza should have used diclofenac DNL instead of diclofenac TRIS, but, unless it is proved the contrary, either Pinza has not tested diclofenac DNL or diclofenac TRIS has better distinctive properties for the use for which it has been selected in Pinza.

Definitely, the study Reference 21 on diclofenac salts offers surprising and unexpected teachings for further reconsideration, such as:

a) no "diclofenac meglumine" salt has been anticipated (despite the fact that meglumine, an amino alcohol, could have been a candidate, thus meaning that one of the ordinary skill in the art failed to prepare and test "diclofenac with meglumine");

b) these authors have not been motivated to combine diclofenac with meglumine; they failed to disclose the existence, feasibility, or characteristics of this hypothetical salt diclofenac meglumine;

c) the solubility range of those salts presents so wide a range that the less soluble salt of tromethamine (TRIS) is 113-fold less soluble than the most soluble DNL salt of diclofenac;

d) despite supporting "mutual substitutability" Examiner fails to offer any evidence on the feasibility or existence of "diclofenac with meglumine" or of its solubility ranges, which are surprisingly and unexpectedly different even when salts of the same NSAID (diclofenac) are considered.

In conclusion, there is neither scientific data nor objective findings that can reasonably substantiate an expected or a predictable advantage resulting from the substitubility of flurbiprofen with diclofenac or vice versa.

Oromucosal indications - Concentration ranges of Flurbiprofen versus Diclofenac

As previously discussed, there is a lack of support for the substitutability of flurbiprofen with diclofenac (it is akin to saying that iron is a metal so it can be swapped at any time with copper, despite their distinct characteristics that make them suitable for specific applications).

Regardless that flurbiprofen and diclofenac are not homogenous subjects, even the concentration range at which flurbiprofen is used in the present application is from 10 to 20-fold the concentration range of diclofenac in Pinza so that there would not be any kind of obviousness to use from 10 to 20-fold of flurbiprofen (with meglumine) than diclofenac (as tromethamine salt), in view that they are also combined with a different amino compound.

Pinza clearly described that diclofenac tromethamine is used at a concentration from 0.1% to 0.2% (corresponding to 0.071 to 0.142 g of diclofenac/100 ml of water, as stated at page 2 lines 14-15) which means that diclofenac is used at a concentration range from 0.071% to 0.142 %, by contrast the concentration range of flurbiprofen of the instant invention is ranging from 2.0 mg/ml to 4.0 mg/ml, equivalent to a range from 1.0% to 7.5% (10-20-fold higher).

Therefore the above "objective evidence" also proves the different concentrations of the distinct flurbiprofen (present application) and diclofenac (Pinza) and contradicts all Examiner's objections based on a comparable concentration range. Definitely with such differences, there cannot be any overlap of the specific amounts of components.

In conclusion, based on the above, Applicant respectfully suggests that the Examiner has failed to make a prima facie of obviousness with respect to Pinza, when in the compositions that Examiner compared there are distinct components (flurbiprofen and diclofenac having chemical toxicological and pharmacological characters and solubility profiles) in specific amounts (where flurbiprofen has a concentration 10-20-forld more than diclofenac), and in addition each of them is individually combined with a distinct base (meglumine and tromethamine).

pH for oromucosal solutions (buffered or unbuffered solutions)

The reliable pharmaceutical publication "Remington:The Science and Practice in Pharmacy", 20th Ed., 2000 (Reference 23) at page 240 defines "*BUFFERS - The*

terms buffer, buffer solution, no buffered solution, when used with reference to hydrogen-ion concentration of pH, refer to the ability of the system, particularly an aqueous solution, to resist to a change of pH on adding acid or alkali, or on dilution with a solvent." and also better precise "*Characteristic of buffered solutions which undergo small changes of pH on addition of acid or base, is the presence either of a weak acid and a salt of the weak acid or a weak base and a salt of the weak base.*" Remington also indicates that "*Solutions of neutral salts, such as sodium chloride , similarly lack ability to resist change of pH on adding acid or base: such solution are called unbuffered.*"

pH range in the instant invention and in Pinza

A skilled person familiar with oromucosal preparations (either to be used as a mouthwash or to be sprayed in the throat, mouth and gums) knows the importance of the physiological pH of the oral cavity which is between 6.7 and 7.5 (instant description). Therefore it is quite normal that, despite the fact that the instant invention and Pinza contain a different NSAID, both solutions should present a pH range compatible with topical applications into the mouth. Pinza for the composition (oromucosal solution) of diclofenac tromethamine teaches a pH between 7.0 and 8.0. However, in light of the fact that Applicant has amended claim 1 to recite a pH range of 6.5 to 6.9, applicant believes that the rejection is unwarranted.

A skilled person knows that NSAIDs are quite insoluble in water, so it is rather critical to prepare them in a stable solution with a pH range between 6.5 and 7.0.
In such a pH range the NSAID can easily precipitate, which is a criticality to be overcome since a stable solution shall be clear and transparent without precipitation of the active ingredient during the shelf-life period of the medicinal product. The proof that pH 7.0 is a critical limit for any solution of diclofenac salts as well for any other NSAID can be observed at Table 3 (see Reference 22), where only diclofenac TRIS solution shows a pH 7.13, while four (4) salts shows a pH of about 7.5, and three (3) present an excessive pH above 8.0.

Therefore, the fact that the instant invention containing flurbiprofen and meglumine or glucamine can yield and claims a pH range from 6.5 to 7.0 constitutes an unexpected result over the prior art, since the claimed composition allows to solve

this criticality, i.e. to yield a stable solution (without precipitation of the active ingredient) at a pH also from 6.5 to 6.9 thus overcoming the prior art pH range.

Nevertheless, it is worthwhile to consider that in two parts of the description and in claim 1 Pinza describes that "*the pH is adjusted between 7 and 8.*" , and in Example 1 Pinza specifies more precisely that pH 7.6 is obtained by using a "phosphate buffer ("100 g of Mouthwash A contains .... a "*pH 7.8 phosphate buffer ** qs to 100 g*").

Pinza further confirms that the specific "*pH 7.8 phosphate buffer" is the same as that* well known to any skilled artisan [*"one litre of solution in purified water contains dibasic sodium phosphate (5.803 g), anhydrous monobasic potassium phosphate (3.522 g) and 1N sodium hydroxide (18.70 ml)."*].

However, applicant remarks that pH between 7.0 and 8.0 claimed in Pinza for diclofenac tromethamine is not consistent with Reference 22. In fact, in Table 3 a pH 7.13 is reported for saturated solution of diclofenac tromethamine. Consequently, Pinza's lower pH range 7.0 is not consistent with the pH 7.13 reported in Reference 22 for the same diclofenac tromethamine.

By contrast no buffer is contained in the instant invention.

In order to avoid confusion, the term buffer has been removed and has been substituted with the more appropriate term "base."

In-House Communication (Criticality of pH of aqueous solutions of Flurbiprofen)

All above findings and considerations for diclofenac salts show that there are significant differences in terms of solubility, pH, and dissociation, not to mention differences among the diclofenac salts (TRIS, DNL, AMP, AMPD, BA, tBA), thus confirming that those distinct behaviors would be unexpected and unpredictable. Therefore, any suggestion that there exists a motivation to interchangeably use them lacks support or a reasonable expectation of success.

Similarly, the In-house Communication (enclosed Reference 23) shows the unexpected, unpredictable and substantially distinct results of flurbiprofen when combined with meglumine or NaOH (sodium hydroxide) or even tromethamine (TRIS) in term of pH and of stability of the resulting solutions. The combination of flurbiprofen and meglumine (instant invention) shows that this allows the formulation

to overcome the criticality of the aquesous solution which is stable at pH 6.8, which is within the claimed pH range from 6.5 to 6.9. As further evidence of the unpredictability of the combinations, the combination of flurbiprofen with the base NaOH (sodium hydroxide) does not give the expected and predictable results (as those obtained for one of the best seller salt diclofenac sodium). In fact, after a clear and transparent solution is obtained by heating at 50°C, cooling gives a precipitation (crystals) which is not compatible with a pharmaceutical use of the solution.

Therefore the physico-chemical conditions to yield a stable aqueous solution are substantially different from each active ingredient from the other and even among salts of the same ingredient, so that the most suitable conditions for one of them cannot be automatically or simply applied to another, in view that real experimental findings are unpredictable and often not suitable as expected. Consequently, Applicant rebuts the prima facie obviousness assertion on theoretical motivations such as those adopted for the refusal.

Considerations Based on MPEP

MPEP 2144.07 (Office Action page 6) – In Sinclair & Carroll Co v. Interchemical Corp. In Sinclair, there are two variables "ink" and "solvent" and only solvent has been changed. The instant invention presents at least four variables: flurbiprofen (which cannot simply be substituted with diclofenac for the reasons previously explained), concentration range (10-20-fold) of flurbiprofen, and meglumine to yield a claimed pH range from 6.5 to 6.9. While in Sinclair it is feasible to modify the solvent to yield the same result, the teachings of Pinza and Caldwell cannot be suitably applied to the instant invention since it has been proved that doing so would yield opposite results to those expected (precipitation or unsuitable pH incompatible with the physiological range of the mouth). Therefore this obviousness criteria is traversed.

MPEP 2144.05 (correct reference is 2144.06) (Office Action page 6) – Examiner sentence that : " *it would have been motivated ... to utilize the flurbiprofen in combination with the diclofen since...*" does not correspond to the invention in absence of any indication that applicant has proposed to combine flurbiprofen with diclofenac.

Applicant rebuts any criteria of obviousness in re Kerkhoven, where two conventional detergents have been mixed to form a third composition, in view that the instant invention does not combine flurbiprofen and diclofenac.

MPEP 2144.05 (Office Action page 6) – Applicant rebuts the assertion of obviousness based on in re Wertheim, Woodruff, Geisler referring that "*the claimed ranges and prior art ranges do not overlap but are closed enough...*" in view that Pinza clearly described that diclofenac tromethamine is used at a concentration from 0.1% to 0.2% (page 2 lines 14-15) while, on the contrary, flurbiprofen of the instant invention is ranging from 1.5 mg/ml to 7.5 mg/ml equivalent to a range from 1.0% to 7.5% , which is 10-20-fold higher than the opposed art ranges. Objectively, one cannot confuse 10-20 fold higher with "close enough".

MPEP 2144.05 (Office Action page 8) – *Prima facie* obviousness based on in re *Titanium Metals Corp.* is rebutted by applicant in view that once it has been demonstrated that diclofenac is not a substituted equivalent of flurbiprofen, it is redundant to further argue this topic. The described and claimed range of flurbiprofen of the instant invention is 10-20-fold that of diclofenac and objectively they are not even close to each other.

MPEP 2144.05 (Office Action page 8) – Applicant rebuts *prima facie* obviousness based on in *re Aller* and *Woodruff* in view that once it has been demonstrated that diclofenac is not a substituted equivalent of flurbiprofen, the applicant has also shown that there is more than one particular critical range that has been overcome in the invention over the prior art (flurbiprofen combined with meglumine, now claimed pH range from 6.5 to 6.9 and active substance range from 2.0 to 4.0 mg/ml).

MPEP § 716.02 and 716-02(g) - Definitely in view of the instant invention teaches away from the prior art for all those above mentioned criticalities. In fact, the prior art has not anticipated an aqueous solution containing flurbiprofen with meglumine, being flurbiprofen claimed at a concentration from 2.0 mg/ml to 4.0 mg/ml to yield a stable solution with a claimed pH critical range from 6.5 to 6.9.

In view of the above Applicant submits that the presumption of obviousness based on the Examiner's current reasoning is without support.

Considering the teaching to be drawn from the opposed prior art and the facts and observations here above evidenced, it is not seen in which way the artisan could modify or otherwise optimize in an obvious way the disclosed prior art in order to anticipate or render obvious the instant invention.

In conclusion Applicant believes that, in light of the claim amendments and arguments made herein, the present claims are in condition for allowance. Applicant hopes that, in the light of the foregoing, the Examiner will now feel able to issue a favorable report.

Respectfully submitted,

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